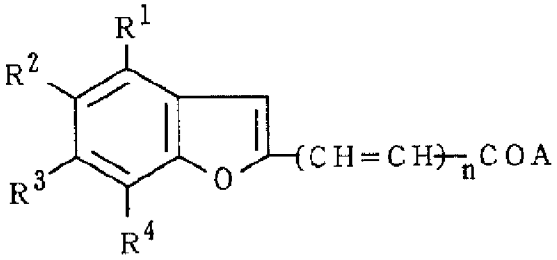
DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Industrial Application]This invention relates to the hepatopathy depressant which contains a useful new benzofuran derivative and this for prevention of a hepatopathy, and a therapy.
[0002]
[Description of the Prior Art]The origin of a hepatopathy is not uniform, and the acute and chronic hepatopathy by a virus, alcohol, a drug, poison, a hepatic circulation system obstacle, biliary obstruction, etc. becomes entangled, and it causes illnesses, such as a hepatic fever, drug intoxication hepatitis, alcoholic hepatitis, congestive hepatitis, a bile depression belt, a fatty liver, icterus, and liver cirrhosis. Under the present circumstances, prevention and the therapy of these illnesses are very difficult.
[0003]Glycyrrhizin pharmaceutical preparation is known as drugs used for prevention and the therapy of a hepatopathy. However, side effects, such as a fake aldosterone action, occur. Intravenous administration is required for the drug effect manifestation, and it is invalid in internal use.
[0004]For prevention and the therapy of a hepatopathy, as a useful compound to JP,2-124884,A. They are indicated by N-substituted amide derivatives, such as N-(3,4-methylenedioxyphenacyl) acetamide, and to JP,2-138160,A. N-substituted amide derivatives, such as N-methyl-N-phenacyl butaneamide and N-(4-fluorophenacyl)-N-methylpentanamide, are indicated. N-substituted amide derivatives, such as 3-(1,1-diethoxy- 2-hexanamide ethyl) pyridine, are indicated by JP,2-145572,A.
[0005]
[Problem(s) to be Solved by the Invention]The purpose of this invention is to provide prevention of a hepatopathy, and a therapy with a useful new benzofuran derivative.
[0006]Other purposes of this invention are to provide the new hepatopathy depressant which has prevention and the curative effect of a high hepatopathy also by internal use.
[0007]
[Elements of the Invention]Various benzofuran derivatives are compounded that this invention persons should develop a drug effective in prevention and a therapy of a hepatopathy, As a result of doing a pharmacological activity examination, in an acetaminophen acuteness liver injury model, a specific benzofuran derivative which has a carbamoyl group showed strong hepatopathy depressant action, found out that it was useful as prevention of a hepatopathy, and a treating agent, and completed this invention.
[0008]That is, this invention is following formula [I].

[0009]
[Formula 2]



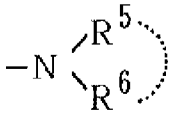
[I]

(Among a formula, A shows a mono- substituted amino group or the JI substituted amino group which may be annular, and;R^1, R^2, R^3, and R^4) any adjoining two join together, form a methylenedioxy group, and others show a hydrogen atom --;n -- the integer of 0-2 -- being shown -- the benzofuran derivative expressed or its salt is provided.

[0010]This invention provides the hepatopathy depressant which contains again the benzofuran derivative expressed with said formula [I], or its salt.

[0011]Said substituent A is a following formula. [0012]

[Formula 3]



(Among a formula, R^5 and R^6 may be the same or different, a hydrogen atom, the low-grade alkyl group which may be replaced, a cycloalkyl group, or an aryl group may be shown, and R^5 and R^6 may form the ring with the adjoining nitrogen atom.) however, R^5 and R^6 -- simultaneous -- a hydrogen atom -- it is not -- it is expressed.

[0013]To the low-grade alkyl group in said R^5 and R^6. Methyl, ethyl, propyl, isopropyl, butyl, isobutyl, s-butyl, t-butyl, pentyl, isopentyl, neopentyl one, t-pentyl, The alkyl group of the straight chain of the carbon numbers 1-6, such as 1-ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, and 2-ethylbutyl group, or the letter of branching is contained.

[0014]The cycloalkyl group of the carbon numbers 3-8 of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, a cycloheptyl group, etc. is contained in a cycloalkyl group.

[0015]A phenyl group and a naphthyl group are contained in an aryl group.

[0016]Said low-grade alkyl group and the aryl group may be replaced by 1 or two or more substituents. As such a substituent, methoxy and ethoxy ** propoxy, isopropoxy, Butoxy, isobutoxy, s-butoxy, t-butoxy, pentyloxy, Isopentyloxy, t-pentyloxy, neopentyl oxy, hexyloxy, Isohexyloxy, 1,1-dimethylbutoxy, 2,2-dimethylbutoxy, Lower alkoxy groups, such as a 3,3-dimethylbutoxy group (when it has two or more alkoxy groups as a substituent) Even if the alkyl group of two lower alkoxy groups joins together and it forms the methylene chain, good; methylthio, Low-grade alkylthio groups, such as ethylthio, isopropylthio, butylthio, and a hexyl thio group; Amino **. Methylamino, ethylamino, isopropylamino, t-butylamino, Dimethylamino, diethylamino, diisopropylamino, anilino, No replacing or substituted amino group; hydroxyls, such as 1-pyrrolidinyl, piperidino, and a morpholino group; Fluoride, Low-grade alkyl groups, such as halogen atom; methyl, such as chlorine and bromine, ethyl, propyl, isopropyl, butyl, t-butyl, neopentyl one, and an isohexyl

group; Cyclopropyl, cyclopentyl, Cycloalkyl groups, such as a cyclohexyl group; aryl groups, such as phenyl and a naphthyl group, etc. are mentioned.

[0017]Said R^5 and R^6 may form the ring with the adjoining nitrogen atom, and a five-membered ring and six membered-rings are mentioned as such a ring, for example. In the five-membered ring and 6 membered-ring group which are formed with a nitrogen atom. Unsaturation heterocycle groups, such as saturated heterocycle group;1-pyrrolyl, such as 1-pyrrolidinyl, piperidino, morpholino, 1-piperazinyl, and a thiomorpholino [tetrahydro 1,4-thiazine 4-yl] basis, 1-imidazolyl, and 1-pyrazolyl group, are contained.

[0018]The aryl group etc. which may be replaced by alkoxy groups, such as alkyl groups, such as alkyl group; methyl, such as methyl, ethyl, and an isopropyl group, and an ethyl group, methoxy, and an ethoxy basis, etc. may combine with the carbon atom on the ring of said heterocycle group, and the nitrogen atom. As such a heterocycle group, 1-(4-methyl) piperazinyl, 1-(4-phenyl) piperazinyl, a 1-(4- (2-methoxypheny)) piperazinyl group, etc. are illustrated.

[0019]In a desirable mono- substituted amino group, methylamino, ethylamino, propylamino, The lower alkylamino group of the carbon numbers 1-6 of an isopropylamino and isobutylamino **t-butylamino group etc.; (2-methoxy ethyl) Amino **. (3-methoxy propyl) Amino ** (3-ethoxypropyl) amino **. (3-isopropoxy propyl) Amino ** (3-butoxypropyl) amino **. (3-isobutoxypropyl) The amino group whose carbon numbers of alkoxy portions, such as an amino group, and an alkyl part are 1-6, respectively (low-grade alkoxy low-grade alkyl); Phenylamino, (2,3-methylenedioxyphenyl) Arylamino groups, such as an amino ** (3,4-methylenedioxyphenyl) amino group, etc. are contained.

[0020]In a desirable JI substituted amino group, dimethylamino, diethylamino, N-methylethylamino, N-methyl isopropylamino and N-methylisobutylamino **N-methyl-(t-butyl) amino **. N and N-JI lower alkylamino group whose carbon numbers of each alkyl part, such as N-methylisopentylamino group, are 1-6; 6 member heterocycle groups, such as piperidino, morpholino, thiomorpholino, 1-piperazinyl, and a 1-(4- (2-methoxypheny)) piperazinyl group, etc. are contained.

[0021]In the compound expressed with said formula [I], R^1, R^2, Any two bases which adjoin among R^3 and R^4, i.e., R^1, R^2 and R^2, R^3 or R^3, and R^4 join together, and a methylenedioxy group is formed. And other bases which do not form the methylenedioxy group show a hydrogen atom. The compound which has such substituent R^1, R^2, R^3, and R^4 has large hepatopathy depressant action.

[0022]In the compound of this invention, although n can be freely chosen for the integer of 0-2, n of a desirable compound is a compound of 0 or 1.

[0023]Any compound is contained in this invention although the geometric isomerism of Sis and a transformer exists about the double bond of -CH=CH-.

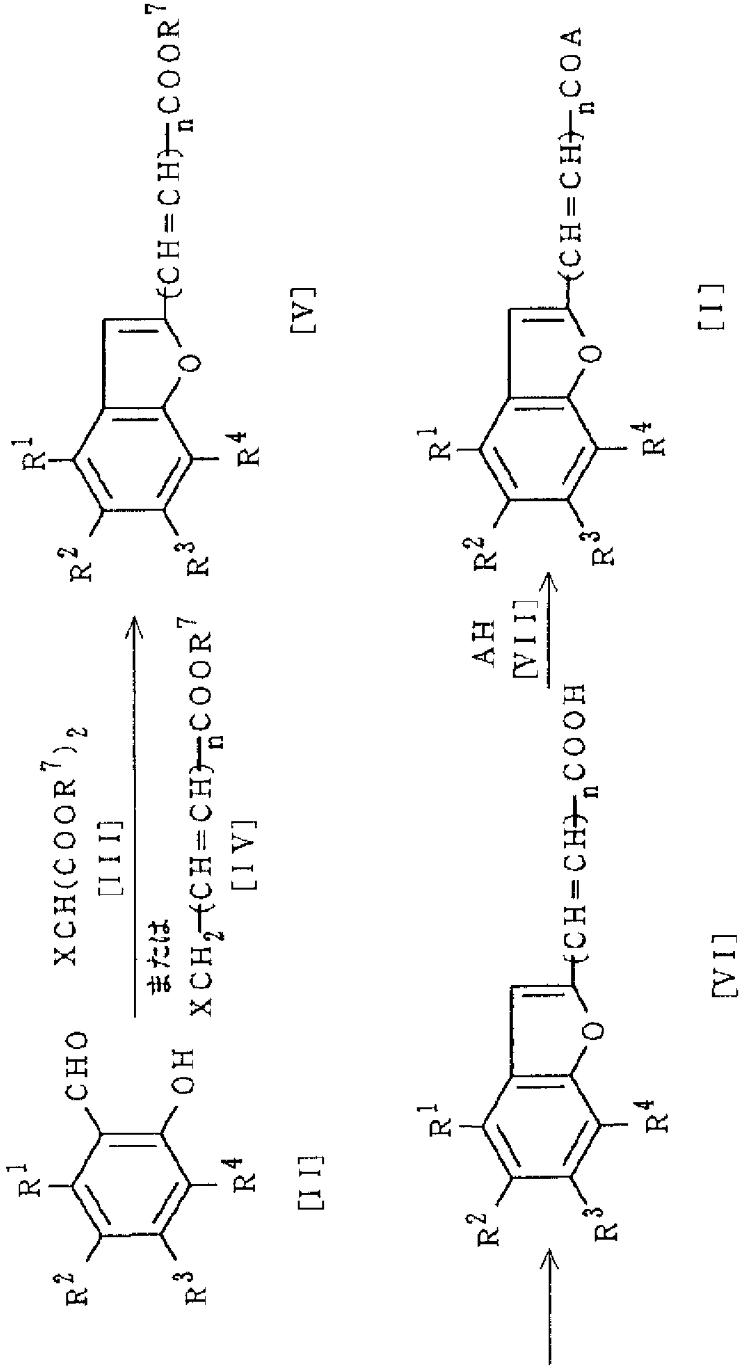
[0024]When the compound expressed with formula [I] shows basicity, when said A is no replacing or a substitution amino alkylamino group, a 1-piperazinyl group, etc., acid addition salt can be formed, for example. Such a salt is also contained in this invention.

[0025]In the acid which forms said salt, chloride, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, Inorganic acid, such as boric acid; Formic acid, acetic acid, propionic acid, trifluoroacetic acid, Organic acid, such as oxalic acid, succinic acid, maleic acid, lactic acid, malic acid, tartaric acid, salicylic acid, gallic acid, methanesulfonic acid, trifluoromethanesulfonic acid, benzenesulfonic acid, and p-toluenesulfonic acid, is contained.

[0026]The compound expressed with said formula [I] is compoundable by the method shown by the following reaction process formula, for example.

[0027]

[Formula 4]



(A, R^1, R^2, R^3, R^4, and n show the same meaning as the above among a formula, R^7 shows a low-grade alkyl group and X shows a halogen atom) As a low-grade alkyl group in said R^7, The alkyl group of the carbon numbers 1-6, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, and a hexyl group, is mentioned. An alkyl group especially a methyl group, an ethyl group, etc. of the carbon numbers 1-3, such as methyl, ethyl, and a propyl group, are used suitably among these.

[0028]Fluoride, chlorine, bromine, and iodine are contained in the halogen atom in said X. Pressure of business especially of chlorine or bromine is carried out among these.

[0029]2-hydroxybenzaldehyde expressed with formula [II] and the halogenated-aliphatics carboxylate which are expressed with the halo malonic ester or formula [IV] expressed with formula [III] are made to react, and the carboxylate which has a benzofuranyl group expressed with formula [V] is obtained.
[0030]2-hydroxybenzaldehyde expressed with formula [II] has a methylenedioxy group. 2-hydroxy-3,4-methylenedioxybenzaldehyde, 2-hydroxy-4,5-methylenedioxybenzaldehyde, and 2-hydroxy-5,6-methylenedioxybenzaldehyde are contained in such a compound.
[0031]As halo malonic ester [III], chloro methyl malonate, chloroethyl malonate, bromo methyl malonate, bromoethyl malonate, etc. are mentioned, for example.
[0032]As halogenated-aliphatics carboxylate [IV], Methyl chloroacetate, ethyl chloroacetate, methyl bromoacetate, ethyl bromoacetate, 4-chlorocrotonic acid methyl, 4-chloroethyl crotonate, 4-bromocrotonic acid methyl, 4-bromoethyl crotonate, 6-chloro-2,4-hexadiene acid methyl, 6-chloro-2,4-hexadiene acid ethyl, 6-bromo-2,4-hexadiene acid methyl, 6-bromo-2,4-hexadiene acid ethyl, etc. are illustrated.
[0033]The above-mentioned reaction is usually performed under existence of a base. An inorganic base or an organic base can be used as a base. As an inorganic base, hydroxide; magnesium hydroxide of alkaline metals, such as sodium hydroxide, a potassium hydrate, and lithium hydroxide, Hydroxide of alkaline-earth metals, such as calcium hydroxide, strontium hydroxide, and barium hydroxide; Sodium carbonate, Carbonate of alkaline metals, such as potassium carbonate and lithium carbonate; carbonate of alkaline-earth metals, such as magnesium carbonate, calcium carbonate, and barium carbonate, etc. are mentioned. As an organic base, triethylamine, tripropylamine, pyridine, Picoline, N.N-dimethylaniline, 4-dimethylaminopyridine, N-methylmorpholine, N-methyl piperidine, 1,5-diazabicyclo [4.3.0.] nonene- 5, 1,4-diazabicyclo [2.2.2] octane, 1, and 8-diazabicyclo [5.4.0] undecene 7 etc. are mentioned. Carbonate of alkaline metals, such as potassium carbonate, etc. are used suitably among these.
[0034]A reaction is usually performed at a room temperature - the flowing-back temperature of a solvent among an inert solvent. As a solvent, for example Aromatic hydrocarbon; carbon tetrachlorides, such as benzene, toluene, and xylene, Halogenated hydrocarbon, such as chloroform, dichloromethane, and 1,2-dichloroethane; Pentane, Alicycle fellows hydrocarbon, such as aliphatic hydrocarbon; cyclohexane, such as hexane and octane, and a methylcyclohexane; Diethylether, Ether, such as dimethoxyethane, dioxane, and a tetrahydrofuran; Acetone, ketone [, such as methyl ethyl ketone,]; -- aprotic polar solvent; carbon bisulfide; water;, such as acetonitrile, N.N-dimethylformamide, dimethyl sulfoxide, and hexamethylphosphoric triamide, -- the mixed solvent of these, etc. are mentioned.
[0035]In this reaction, when the compound of formula [I] which is an object compound is n= 0 and the compound of formula [I] is n= 1 or 2 again about the compound of formula [III] or formula [IV], especially the compound of formula [III], the compound of formula [IV] can be used.
[0036]Next, carboxylate [V] obtained by said reaction is hydrolyzed, and corresponding carboxylic acid [VI] is obtained.
[0037]The hydrolysis can use conventional alkali hydrolysis, acidolysis, or neutral hydrolysis method.
[0038]When based on an alkali hydrolysis method, it can hydrolyze easily by using alkali, such as a potassium hydrate and sodium hydroxide, for example among alcohol solvents, such as methanol and ethanol.
[0039]The generated above-mentioned carboxylic acid [VI] can remain as it is, or can be used by a next process as the reactive derivative.

[0040]Carboxylic acid [VI] obtained by the aforementioned reaction or its reactive derivative, and the 1st class or secondary amine expressed with formula [VII] corresponding to the substituent A is made to react, and the compound of formula [I] which is an object compound is obtained.
[0041]As a reactive derivative of said carboxylic acid [VI], For example, an active ester; acid anhydride with acid halide; acid azide;N-imide hydroxysuccinate, such as an acid chloride and an acid smell ghost, N-hydroxybenzotriazol, p-nitrophenol, etc.; a mixed acid anhydride with alkyl carbonic acid, p-toluenesulfonic acid, etc., etc. are mentioned.
[0042]When using said carboxylic acid [VI], a reaction is usually performed under existence of a dehydration condensation agent.
[0043]As a dehydration condensation agent, BIRUSU Meyer's reagents, such as thionylchloride, phosphorus oxychloride, phosphorous pentachloride, and dimethylannmonium (chloromethylene) chloride, dicyclohexylcarbodiimide (DCC), 2,2'-pyridyl disulfide triphenyl phosphine, etc. are illustrated.
[0044]The reaction of said carboxylic acid [VI] or its reactive derivative, and the 1st class or secondary amine [VII] is usually performed at -20 ** - the flowing-back temperature of a solvent among an inert solvent. Basic solvents, such as piperidine, triethylamine, pyridine, picoline, quinoline, etc. besides the aforementioned solvent as a solvent; ester species, such as methyl acetate, ethyl acetate, isopropyl acetate, butyl acetate, amyl acetate, cellosolve acetate, and ethyl propionate, etc. can be used.
[0045]It is more preferred to perform the above-mentioned reaction under existence of a basic compound. The aforementioned base etc. can be used as a basic compound.
[0046]The method of making said amine [VII] acting on said carboxylate [V] directly, and obtaining object compound [I] as an exception method for obtaining the compound of this invention is also employable. In this case, the catalyst usually used for ester exchange reactions, such as an alkoxide of an alkaline metal, can be used as a catalyst.
[0047]When it changes into the salt by a conventional means when object compound [I] is obtained by the above-mentioned method, and obtained as a salt of compound [I], it can change into compound [I] itself by a conventional means.
[0048]Isolation refining of the benzofuran derivative expressed with said formula [I] can be carried out by presenting conventional separation refinement means, for example, recrystallization, solvent extraction, distillation, chromatography, etc. with the resultant acquired by said method.
[0049]The hepatopathy depressant of this invention contains the compound expressed with said formula [I], or its salt. As shown by the following examination, in an acetaminophen acuteness liver injury model, powerful hepatopathy depressant action is shown, and the compound expressed with said formula [I] and its salt are low toxicity, and their safety is high. Therefore, the safe hepatopathy depressant for mammalians, such as Homo sapiens, is provided by this invention.
[0050]Although the content in particular of the compound expressed with formula [I] or its salt is not restricted, it is usually about 1-80 mg preferably 0.1-500 mg per administration unit. Although the dose of the compound expressed with formula [I] or its salt changes with the kind of compound, a route of administration, age, the grade of a hepatopathy, kinds of liver disease, etc., an adult 1 Japanese hit and 0.1-500 mg of abbreviation are usually about 1-100 mg preferably. The frequency of administration in particular per day is not restricted, but can carry out another **** administration at 1 time or several times.
[0051]The hepatopathy depressant of this invention has the special feature that the drug effect effect is

effectively revealed also by internal use. Therefore, medication methods may be taking orally and parenteral any.

[0052]As a dosage form, liquids and solutions, such as solid preparation; suspension, such as a tablet, a granule, powder medicine, a pill, and a capsule, an emulsion, injections, and an infusion solution, are mentioned.

[0053]In preparation of the solid preparations for taking orally, a conventional ingredient, for example, starch, milk sugar, Sugars, such as sucrose, mannitol, and cornstarch, crystalline cellulose, Excipients, such as carboxymethyl cellulose and silicic acid; Polyvinyl alcohol, A polyvinyl pyrrolidone, polyvinyl ether, ethyl cellulose, gum arabic, Tragacanth, gelatin, hydroxypropylcellulose, calcium citrate, Lubricant, such as binding material; magnesium stearates, such as dextrin and pectin, talc, and a polyethylene glycol; disintegrator, such as carboxymethyl-cellulose calcium, a collapse auxiliary agent, stabilizer, colorant, etc. can be used.

[0054]Surface-active agents, such as a conventional ingredient, for example, water, ethyl alcohol, ethylene glycol, glycerin, and polyoxyethylene sorbitan fatty acid ester, grape sugar, amino acid, a soothing agent, a solubilizing agent, a buffer, colorant, a preservative, sweetners, etc. can be used for preparation of liquids and solutions.

[0055]The liver-problems depressant of the above-mentioned dosage forms can be manufactured in accordance with a conventional method using the above-mentioned addition ingredient by the compound or its salt, and necessity for formula [I].

[0056]The depressant action of a hepatopathy is usually judged by the depressor effect of the sample compound to the impaired liver function of the test animal which prescribed the hepatopathy inducer for the patient. As a hepatopathy inducer, a carbon tetrachloride, D-galactosamine, acetaminophen, etc. can be used, for example.

[0057]

[Effect of the Invention]By this invention, the new molecular entity expressed with formula [I] and its salt are provided, and these compounds are useful for prevention of a hepatopathy, and a therapy.

[0058]The compound expressed with said formula [I] and its salt show high depressant action to the rise of an ALT activity value in an acetaminophen acuteness liver injury model also by internal use. Therefore, the hepatopathy depressant of this invention is useful as prevention and the remedy of the hepatopathy by taking orally and parenteral administration.

[0059]

[Example]Below, based on an example and the example of an experiment, this invention is explained more at details.

[0060]The reference example 16-methoxy methoxy-2,3-methylenedioxybenzaldehyde 15.9g (50.5 millimol) was melted in 250 ml of methanol, 40 ml of chloride was added 10%, and it flowed back for 10 minutes. After cooling reaction mixed liquor radiationally, it condensed, and 500 ml of ether and 500 ml of water were added and extracted. The organic layer was condensed, the silica gel column was given, after dichloromethane eluted and refined, it recrystallized [methanol] and 2-hydroxy-5,6-methylenedioxybenzaldehyde [IIb]9.7g of the yellow needle shape crystal was obtained (77% of yield).

[0061]melting point: -- 117-118 ** ultimate analysis: -- a $C_8H_6O_4$ theoretical value -- the (%):C,57.84:H,3.64 actual-measurement (%):C,57.85:H,3.77 ^{1}H-nuclear magnetic resonance spectrum (heavy chloroform)

delta:10.41 (1H, s, -OH). 10.13 (1H, s, -CHO), 6.97 (1H,d,J=8.6Hz), 6.36 (1H,d,J=8.6Hz), and 6.07 (2H, s, -OCH_2O-)

The infrared absorption spectrum (KBr) nu (cm^{-1}):3425,1670,1640,1464, 1242,1190,1050 reference-example 22-hydroxy-4,5-methylenedioxybenzaldehyde [IIa]29.0g, 47.9g of bromodiethyl malonate and the potassium carbonate 72.5g were added to 500 ml of anhydrous methyl ethyl ketone, and it flowed back for 40 hours. Except for the insoluble matter, it condensed after ending reaction through reaction mixed liquor to cerite. The crystal which added ethanol to concentration residue and was produced was separated, it recrystallized [ethanol], and 2-(5,6-methylenedioxy) benzo[b] furancarboxylic acid ethyl ester [Va]26.5g of the colorless needle shape crystal was obtained (65% of yield).

[0062]melting point: -- 85-86 ** ultimate analysis: -- a $C_{12}H_{10}O_5$ theoretical value -- the (%):C,61.54:H,4.30 actual-measurement (%):C,61.36:H,4.15 ^{1}H-nuclear magnetic resonance spectrum (heavy chloroform) delta:7.43 (1H, s). 7.05 (1H, s), 6.89 (1H, s), 6.04 (2H, s, -OCH_2O-), 4.42 (2H,q,J=7.0Hz), 1.41 (3H,t,J=7.0Hz)

Reference example 32-hydroxy-5,6-methylenedioxybenzaldehyde [IIb] 9.7 g, 16.0g of bromodiethyl malonate, and the potassium carbonate 24.3g were added to 200 ml of anhydrous methyl ethyl ketone, and it reacted like the reference example 2. Output was ******ed from ethanol and 2-(4,5-methylenedioxy) benzo [b] furancarboxylic acid ethyl ester [Vb]8.6g of the colorless needle shape crystal was obtained (63% of yield).

[0063]melting point: -- 106-107 ** ultimate analysis: -- $C_{12}H_{10}O_5$ theoretical-value (%):C,61.54:H,4.30 actual measurement (%):C,61.26:H,4.11 ^{1}H-nuclear-magnetic-resonance-spectrum (heavy chloroform) delta:7.46. (1H,d,J=0.8Hz), 7.06 (1H, dd, J= 0.8, 8.6 Hz), 7.00 (1H,d,J=8.6Hz), 6.09 (2H, s, -OCH_2O-), 4.44 (2H,q,J=7.0Hz), 1.43 (3H,t,J=7.0Hz)

Infrared-absorption-spectrum (KBr) nu (cm^{-1}):1722 (C=O), 1270 (C-CO-O), 1185, 1050, 950 (-OCH_2O-)

Reference example 42-hydroxy-3,4-methylenedioxybenzaldehyde [IIc] 18.7 g, 30.9g of bromodiethyl malonate, and the potassium carbonate 46.8g were added to 320 ml of anhydrous methyl ethyl ketone, and it reacted like the reference example 2. Output was ******ed from ethanol and 2-(6,7-methylenedioxy) benzo [b] furancarboxylic acid ethyl ester [Vc]13.1g of the colorless needle shape crystal was obtained (50% of yield).

[0064]melting point: -- 94.7 -95.7 ** ultimate analysis: -- a $C_{12}H_{10}O_5$ theoretical value -- the (%):C,61.54:H,4.30 actual-measurement (%):C,61.51:H,4.50 ^{1}H-nuclear magnetic resonance spectrum (heavy chloroform) delta:7.49 (1H, s). 7.17 (1H,d,J=8.4Hz), 6.93 (1H,d,J=8.4Hz), 6.09 (2H, s, -OCH_2O-), 4.43 (2H,q,J=7.1Hz), 1.42 (3H,t,J=7.2Hz)

2-(5,6-methylenedioxy) benzo[b] furancarboxylic acid ethyl ester [Va]12g obtained by the infrared absorption spectrum (KBr) nu (cm^{-1}):1732,1485,1330,1270 and the 1178,938,920 reference-example 5 reference example 2. It melted in 300 ml of methanol, 10% of potassium hydroxide solutions [500 ml of] were added, and it flowed back for 1 hour. Methanol was distilled out of reaction mixed liquor after ending reaction, the crystal which used chloride acidity and deposited was separated, it recrystallized [ethanol], and 2-(5,6-

methylenedioxy) benzo[b] furancarboxylic acid [VIa]10.1g of the colorless needle shape crystal was obtained (96% of yield).

[0065]The melting point :. 244-246 ** ultimate analysis :. A $C_{10}H_6O_5$ theoretical value. (%) 2-(4,5-methylenedioxy) benzo[b] furancarboxylic acid ethyl ester [Vb]6g (25.6 millimol) obtained by the :C,58.26:H,2.93 actual-measurement (%):C,58.33:H,2.94 reference-example 6 reference example 3 is processed like the reference example 5, Output was ******ed from ethanol and 2-(4,5-methylenedioxy) benzo[b] furancarboxylic acid [VIb]5.1g in the end of non-color powder was obtained (96% of yield).

[0066]melting point: -- 227-240 ** ultimate analysis: -- a $C_{10}H_6O_5$ theoretical value -- the (%):C,58.26:H,2.93 actual-measurement (%):C,58.01:H,2.89 ^{1}H-nuclear magnetic resonance spectrum (heavy acetone) delta:7.54 (1H, s). 7.13 (1H, d, J= 8.6 Hz), 7.11 (1H, d, J= 8.6 Hz), 6.17 (2H, s, -OCH_2O-)

Infrared-absorption-spectrum (KBr) nu (cm^{-1}):3300-2500 (OH), 1708 (C=O), 1418, 1280, 1048, 938 (-OCH_2O-)

Process 2-(6,7-methylenedioxy) benzo[b] furancarboxylic acid ethyl ester [Vc]6.0g obtained by the reference example 7 reference example 4 like the reference example 5, and output is ******ed from ethanol, 2-(6,7-methylenedioxy) benzo[b] furancarboxylic acid [VIc]4.5g of the colorless needle shape crystal was obtained (85% of yield).

[0067]melting point: -- 257-265 ** ultimate analysis: -- a $C_{10}H_6O_5$ theoretical value -- a (%):C,58.26:H,2.93 actual-measurement (%):C,58.01:H,2.94 ^{1}H-nuclear magnetic resonance spectrum (heavy dimethyl sulfoxide.) (It is called heavy DMSO below). delta:7.66 (1H, s), 7.03 (1H, d, J= 8.4 Hz), 7.08 (1H, d, J= 8.4 Hz), 6.20. (2H, s, -OCH_2O-) An infrared absorption spectrum. (KBr) nu (cm^{-1}):3200-2700,1680,1485,1265, 1200,1040,938 reference-example 82-hydroxy-4,5-methylenedioxybenzaldehyde [IIa]12g, 20.52g of 4-bromocrotonic acid ethyl ester and the potassium carbonate 29.76g were added to 360 ml of anhydrous methyl ethyl ketone, and it flowed back for 9 hours. After cooling a reaction mixture radiationally, it let pass and filtered to cerite. Acetone washed filter residue, and a washings and filtrate were set and condensed. After adding 300 ml of water to concentration residue and making it chloride acidity, 300 ml of ethyl acetate extracted. The solid produced by washing an organic layer, drying and condensing is ******ed from ethanol, and it is ethyl of a colorless needle shape crystal. 3-[2-(5,6-methylenedioxy) benzo[b] franc] pro PENATO [Vd] 14.2 g was obtained (76% of yield).

[0068]melting point: -- 153-154 ** ultimate analysis: -- $C_{14}H_{12}O_5$ theoretical-value (%):C,64.61:H,4.65 actual measurement (%):C,64.47:H,4.64 ^{1}H-nuclear-magnetic-resonance-spectrum (heavy chloroform) delta:7.46. (1H,d,J=15.6Hz), 6.95 (1H, s), 6.91 (1H, s), 6.81 (1H, s), 6.44 (1H,d,J=15.6Hz), 6.01 (2H, s, -OCH_2O-), 4.26 (2H,q,J=7.0Hz), 1.33 (3H,t,J=7.0Hz)

It replaces with the infrared absorption spectrum (KBr) nu (cm^{-1}):1720,1640,1458,1320 and 1160,940 reference-example 92-hydroxy-4,5-methylenedioxybenzaldehyde [IIa], 2-hydroxy-5,6-methylenedioxybenzaldehyde [IIb] The output acquired by reacting like the reference example 8 is ******ed from ethanol using 1 g, Ethyl of a yellow needle shape crystal 3-[2-(4,5-methylenedioxy) benzo[b] franc] pro PENATO [Ve] 602 mg was obtained (38% of yield).

[0069]melting point: -- 138-143 ** ultimate analysis: -- $C_{14}H_{12}O_5$ theoretical-value (%):C,64.61:H,4.65 actual measurement (%):C,64.49:H,4.49 ^{1}H-nuclear-magnetic-resonance-spectrum (heavy chloroform) delta:7.49. (1H, d, J= 15.6 Hz), 6.96 (1H, d, J= 8.4 Hz), 6.89 (1H,d,J=8.4Hz), 6.85 (1H, s), 6.55 (1H,d,J=15.6Hz), 6.06 (2H, s, -OCH_2O-), 4.27 (2H,q,J=7.0Hz), 1.34 (3H,t,J=7.0Hz)

It replaces with the infrared absorption spectrum (KBr) nu (cm^{-1}):1708,1638,1480,1300 and 1258,1180,1030,782 reference-example 102-hydroxy-4,5-methylenedioxybenzaldehyde [IIa], 2-hydroxy-3,4-methylenedioxybenzaldehyde [IIc] The output acquired by reacting like the reference example 8 is ******ed from ethanol using 1 g, Ethyl of fine yellow prism ** 3-[2-(6,7-methylenedioxy) benzo[b] franc] pro PENATO [Vf] 736 mg was obtained (47% of yield).

[0070]melting point: -- 107-109 ** ultimate analysis: -- $C_{14}H_{12}O_5$ theoretical-value (%):C,64.61:H,4.65 actual measurement (%):C,64.44:H,4.67 ^{1}H-nuclear-magnetic-resonance-spectrum (heavy chloroform) delta:7.49. (1H, d, J= 15.6 Hz), 7.07 (1H, d, J= 8.4 Hz), 6.88 (1H, s), 6.86 (1H,d,J=8.4Hz), 6.55 (1H,d,J=15.6Hz), 6.09 (2H, s, -OCH_2O-), 4.27 (2H,q,J=7.2Hz), 1.34 (3H,t,J=7.2Hz)

It replaces with the infrared absorption spectrum (KBr) nu (cm^{-1}):1700,1630,1478,1270, 1250,1170,1065,1025, and the 930 reference-example 112-(5,6-methylenedioxy) benzo[b] furancarboxylic acid ethyl ester [Va], Ethyl obtained by the reference example 8 3-[2-(5,6-methylenedioxy) benzo[b] franc] pro PENATO [Vd] 10 g is used, The output acquired by reacting like the reference example 5 was ******ed from methanol, and 3-[2-(5,6-methylenedioxy) benzo[b] franc] propenoic acid [VId]8.11g of the fine yellow needle shape crystal was obtained (91% of yield).

[0071]melting point: -- 272-274 ** ultimate analysis: -- $C_{12}H_8O_5$ theoretical-value (%):C and 62.07:H-3.47 actual-measurement (%):C -- 61.95:H-3.49 ^{1}H-nuclear-magnetic-resonance-spectrum (heavy DMSO) delta:7.48. (1H,d,J=15.8Hz), 7.27 (1H, s), 7.21 (1H, s), 7.15 (1H, s), 6.26 (1H,d,J=15.8Hz), 6.08 (2H, s, -OCH_2O-)

It replaces with the infrared absorption spectrum (KBr) nu (cm^{-1}):3200-2500,1670,1470,1310 and the 1170,940,850 reference-example 122-(5,6-methylenedioxy) benzo[b] furancarboxylic acid ethyl ester [Va], Ethyl obtained by the reference example 9 3-[2-(4,5-methylenedioxy) benzo[b] franc] pro PENATO [Ve] 5 g is used, The output acquired by reacting like the reference example 5 was ******ed from methanol, and 3-[2-(4,5-methylenedioxy) benzo[b] franc] propenoic acid [VIe]4.3g of fine yellow crystalline powder was obtained (96% of yield).

[0072]melting point: -- 255.8 -257.6 ** ultimate analysis: -- $C_{12}H_8O_5$ theoretical-value (%):C and 62.07:H-3.47 actual-measurement (%):C -- 61.96:H-3.46 ^{1}H-nuclear-magnetic-resonance-spectrum (heavy DMSO) delta:7.52. (1H,d,J=15.8Hz), 7.32 (1H, s), 7.10 (1H,d,J=8.6Hz), 7.05 (1H,d,J=8.6Hz), 6.41 (1H,d,J=15.8Hz), 6.14 (2H, s, -OCH_2O-)

An infrared absorption spectrum. (KBr) It replaces with nu (cm^{-1}):3100-2780,1690,1630,1480, 1310,1262,1200,1048, and the 782 reference-example 132-(5,6-methylenedioxy) benzo[b] furancarboxylic acid ethyl ester [Va], Ethyl obtained by the reference example 10 3-[2-(6,7-methylenedioxy) benzo[b] franc] pro PENATO [Vf] 5.85 g is used, The output acquired by reacting like the reference example 5 was ******ed

from methanol, and 3-[2-(6,7-methylenedioxy) benzo[b] franc] propenoic acid [VIf]4.6g of fine yellow crystalline powder was obtained (88% of yield).

[0073]melting point: -- 237.4 -248.4 ** ultimate analysis: -- $C_{12}H_8O_5$ theoretical-value (%):C and 62.07:H-3.47 actual-measurement (%):C -- 61.83:H-3.56 ^{1}H-nuclear-magnetic-resonance-spectrum (heavy DMSO) delta:7.53. (1H,d,J=15.8Hz), 7.32 (1H, s), 7.21 (1H,d,J=8.2Hz), 6.99 (1H,d,J=8.2Hz), 6.33 (1H,d,J=15.8Hz), 6.17 (2H, s, -OCH_2O-)

An infrared absorption spectrum. (KBr) 2-(5,6-methylenedioxy) benzo[b] furancarboxylic acid [VIa]2.0g (9.7 millimol) obtained by nu (cm^{-1}):3150-2800,1670,1480,1280 and the 1075,935 example 1 reference example 5. It was suspended to 20 ml of anhydrous dichloromethane, anhydrous DMF [N.N-dimethylformamide] 400microl and 1.4 ml of thionyl chlorides were added, and it flowed back for 30 minutes. After condensing under decompression of reaction mixed liquor and distilling off a solvent, 30 ml of anhydrous dichloromethane was added to residue, and it was made to dissolve in it.

[0074]15 ml of anhydrous dichloromethane solutions of 1.44 ml (it is the double equivalent to [VIa]) of piperidine were dropped at this solution under ice-cooling. After stirring at a room temperature for 1 hour, 100 ml of ethyl acetate was added to reaction mixed liquor, and dilute hydrochloric acid washed. After washing an organic layer in order of water and a saturation salt solution, it dried and condensed, it recrystallized [ethyl acetate] and 2.1 g of the 1-[2-(5,6-methylenedioxy) benzo[b] franc carbonyl] piperidine of the fine yellow needle shape crystal was obtained (79% of yield).

[0075]melting point: -- 147 ** ultimate analysis: -- $C_{15}H_{15}NO_4$ theoretical-value (%):C and 65.92:H-5.53:N-5.13 actual-measurement (%):C -- a 65.85:H-5.56:N-5.22 ^{1}H-nuclear magnetic resonance spectrum. (Heavy chloroform) delta:7.14 (1H, s), 6.98 (1H, s), 6.96 (1H, s), 6.01 (2H, s, -OCH_2O-), 3.74 (4H, m), 1.70 (6H, m)

It replaces with the anhydrous dichloromethane solution of infrared-absorption-spectrum (KBr) nu (cm^{-1}):1610-1545, 1430, 1280 and 1185, and 940 example 2 piperidine, The output which 8 ml of anhydrous dichloromethane solutions of 1.68 ml (it is the 3 time equivalent to [VIa]) of morpholine were used, and also was acquired by performing the same operation as Example 1 is ******ed from ethyl acetate, 1.7 g of the 4-[2-(5,6-methylenedioxy) benzo[b] franc carbonyl] morpholine of fine yellow prism ** was obtained (64% of yield).

[0076]melting point: -- 137.5-139 ** ultimate analysis: -- $C_{14}H_{13}NO_5$ theoretical-value (%):C and 61.09:H-4.76:N-5.09 actual-measurement (%):C -- a 61.21:H-4.91:N-5.17 ^{1}H-nuclear magnetic resonance spectrum. (Heavy chloroform) delta:7.25 (1H, s), 6.97 (2H, s), 6.02 (2H, s, -OCH_2O-), 3.86 (4H, m), 3.77 (4H, m)

It replaces with the anhydrous dichloromethane solution of infrared-absorption-spectrum (KBr) nu (cm^{-1}):1610-1550, 1425, 1310, 1240, 1105 and 940, and 850 example 3 piperidine, The output which 8 ml of anhydrous dichloromethane solutions of 1.0 ml of thiomorpholine were used, and also was acquired by performing the same operation as Example 1 is ******ed from ethyl acetate hexane, 0.7 g of the 4-[2-(5,6-methylenedioxy) benzo[b] franc carbonyl] thiomorpholine of the fine yellow needle shape crystal was obtained (25% of yield).

[0077]melting point: -- 132-133 ** ultimate analysis: -- $C_{14}H_{13}NO_4S$ theoretical-value (%):C and 57.72:H-

4.50:N-4.81 actual-measurement (%):C -- a 57.69:H-4.54:N-4.84 ^{1}H-nuclear magnetic resonance spectrum. (Heavy chloroform) delta:7.22 (1H, s), 6.97 (2H, s), 6.03 (2H, s, -OCH_2O-), 4.07 (4H, m), 2.75 (4H, m)

It replaces with the anhydrous dichloromethane solution of infrared-absorption-spectrum (KBr) nu (cm^{-1}):1630-1542, 1422, 1295 and 1182, and 940 example 4 piperidine, The output which it let methylamine gas pass for 5 minutes, and also was acquired by performing the same operation as Example 1 was ******ed from ethyl acetate, and 1.61 g of N-methyl-(5,6-methylenedioxy) benzo[b] franc 2-carboxamide of the colorless needle shape crystal was obtained (76% of yield).

[0078]melting point: -- 192.6 -193.6 ** ultimate analysis: -- $C_{11}H_9NO_4$ theoretical-value (%):C and 60.28:H-4.14:N-6.39 actual-measurement (%):C -- a 60.03:H-4.11:N-6.28 ^{1}H-nuclear magnetic resonance spectrum. (Heavy chloroform) delta:7.34 (1H, s), 6.98 (1H, s), 6.93 (1H, s), 6.51 (1H, brs, NH), 6.02 (2H, s, -OCH_2O-), 3.03 (3H,d,J=5.0Hz)

It replaces with the anhydrous dichloromethane solution of infrared-absorption-spectrum (KBr) nu (cm^{-1}):3225-1642, 1588, 1460, 1298 and 1252, and 942 example 5 piperidine, The output which 15 ml of anhydrous dichloromethane solutions of 2.94 ml (it is the 3 time equivalent to [VIa]) of isobutyl amine were used, and also was acquired by performing the same operation as Example 1 is ******ed from ethyl acetate hexane, 2.2 g of N-isobutyl-(5,6-methylenedioxy) benzo[b] franc 2-carboxamide of the colorless needle shape crystal was obtained (87% of yield).

[0079]melting point: -- 121-122 ** ultimate analysis: -- $C_{14}H_{15}NO_4$ theoretical-value (%):C and 64.36:H-5.79:N-5.36 actual-measurement (%):C -- a 64.31:H-5.78:N-5.45 ^{1}H-nuclear magnetic resonance spectrum. (Heavy chloroform) delta:7.34 (1H, s), 6.98 (1H, s), 6.96 (1H, s), 6.54 (1H, brs), 6.02 (2H, s, -OCH_2O-), 3.30 (2H,t,J=6.4Hz), 1.92 (1H, sep, J= 6.6 Hz), 1.00 (6H,d,J=6.8Hz)

It replaces with the anhydrous dichloromethane solution of infrared-absorption-spectrum (KBr) nu (cm^{-1}):3300-2960, 1658, 1640, 1590, 1538, 1460, 1158 and 940, and 650 example 6 piperidine, The output which 8 ml of anhydrous dichloromethane solutions of 2.1 ml of tert-butylamine were used, and also was acquired by performing the same operation as Example 1 is ******ed from ethyl acetate hexane, N of a colorless needle shape crystal -(t-butyl)- (5,6-methylenedioxy) 1.22 g of benzo[b] franc 2-carboxamide was obtained (48% of yield).

[0080]melting point: -- 153.1 -154.1 ** ultimate analysis: -- $C_{14}H_{15}NO_4$ theoretical-value (%):C and 64.36:H-5.79:N-5.36 actual-measurement (%):C -- a 64.32:H-5.92:N-5.29 ^{1}H-nuclear magnetic resonance spectrum. (Heavy chloroform) delta:7.29 (1H, s), 6.98 (1H, s), 6.96 (1H, s), 6.35 (1H, brs, NH), 6.03 (2H, s, -OCH_2O-), 1.49 (9H, s)

It replaces with the anhydrous dichloromethane solution of infrared-absorption-spectrum (KBr) nu (cm^{-1}):3340-1652, 1582, 1522, 1460, 1296, 1255, 1152 and 940, and 859 example 7 piperidine, The output which 8 ml of anhydrous dichloromethane solutions of 2.32 ml of N-isobutyl-N-methylamine were used, and also was acquired by performing the same operation as Example 1 is ******ed from ether hexane, 1.9 g of N-isobutyl-N-methyl-(5,6-methylenedioxy) benzo[b] franc 2-carboxamide of the colorless needle shape crystal

was obtained (70% of yield).

[0081]melting point: -- 88.7 -89.7 ** ultimate analysis: -- $C_{15}H_{17}NO_4$ theoretical-value (%):C and 65.44:H-6.22:N-5.09 actual-measurement (%):C -- a 65.48:H-6.31:N-5.00 ^{1}H-nuclear magnetic resonance spectrum. (Heavy chloroform) delta:7.23 (1H, s), 6.99 (1H, s), 6.98 (1H, s), 6.02 (2H, s, -OCH_2O-), 3.47 (2H, brs), 3.28-3.12 (3H, brm), 2.07 (1H, quint, J= 6.6 Hz), 0.94 (6H,d,J=6.6Hz)

It replaces with the anhydrous dichloromethane solution of infrared-absorption-spectrum (KBr) nu (cm^{-1}):1618-1542, 1460, 1318 and 1178, and 942 example 8 piperidine, The output which 8 ml of anhydrous dichloromethane solutions of 2.0 ml of 3-methoxypropylamine were used, and also was acquired by performing the same operation as Example 1 is ******ed from ethyl acetate, N of colorless prism ** -(3-methoxy propyl)- (5,6-methylenedioxy) 2.0 g of benzo[b] franc 2-carboxamide was obtained (74% of yield).

[0082]melting point: -- 123.7 -124.7 ** ultimate analysis: -- $C_{14}H_{15}NO_5$ theoretical-value (%):C and 60.64:H-5.45:N-5.05 actual-measurement (%):C -- a 60.78:H-5.38:N-5.11 ^{1}H-nuclear magnetic resonance spectrum. (Heavy chloroform) delta:7.32 (1H, s), 7.02 (1H, brs, NH), 6.98 (1H, s), 6.95 (1H, s), 6.02 (2H, s, -OCH_2O-), 3.62-3.52 (4H, m), 3.40 (3H, s), 1.90 (2H, quint, J= 6.1 Hz)

It replaces with the anhydrous dichloromethane solution of infrared-absorption-spectrum (KBr) nu (cm^{-1}):3320-1650, 1590, 1530, 1462, 1296, 1250, 1120, 1038 and 950, and 863 example 9 piperidine, The output which 8 ml of anhydrous dichloromethane solutions of 2.67 ml of 3-isopropoxy propylamine were used, and also was acquired by performing the same operation as Example 1 is ******ed from ethyl acetate hexane, N of a colorless needle shape crystal -(3-isopropoxy propyl)- (5,6-methylenedioxy) 2.1 g of benzo[b] franc 2-carboxamide was obtained (71% of yield).

[0083]melting point: -- 95.5 -96.3 ** ultimate analysis: -- $C_{16}H_{19}NO_5$ theoretical-value (%):C and 62.94:H-6.27:N-4.59 actual-measurement (%):C -- a 63.06:H-6.13:N-4.63 ^{1}H-nuclear magnetic resonance spectrum. (Heavy chloroform) delta:7.51 (1H, brs, NH), 7.31 (1H, s), 6.98 (1H, s), 6.90 (1H, s), 6.01 (2H, s, -OCH_2O-), 3.70-3.55 (5H, m), 1.88 (2H, quint, J= 5.8 Hz), 1.25 (6H,d,J=6.0Hz)

It replaces with the anhydrous dichloromethane solution of infrared-absorption-spectrum (KBr) nu (cm^{-1}):3280-1638, 1570, 1465, 1310, 1260, 1162, 1040 and 950, and 863 example 10 piperidine, The output which 15 ml of anhydrous dichloromethane solutions of 2.8 g (it is the 3 time equivalent to [VIa]) of 1-(2-methoxypheny) piperazines were used, and also was acquired by performing the same operation as Example 1 is ******ed from ethyl acetate hexane, 2.3 g of the 1-(2-methoxypheny)-4-[2-(5,6-methylenedioxy) benzo[b] franc carbonyl] piperazines of the colorless needle shape crystal were obtained (85% of yield).

[0084]melting point: -- 150-151 ** ultimate analysis: -- $C_{21}H_{20}N_2O_5$ theoretical-value (%):C and 66.31:H-5.30:N-7.36 actual-measurement (%):C -- a 66.42:H-5.23:N-7.38 ^{1}H-nuclear magnetic resonance spectrum. (Heavy chloroform) delta:7.25 (1H, s), 7.09-6.88 (6H, m), 6.02 (2H, s, -OCH_2O-), 4.04 (4H, brs), 3.90 (3H, s, OCH3), 3.15 (4H,t,J=5.0Hz)

It replaces with the anhydrous dichloromethane solution of infrared-absorption-spectrum (KBr) nu (cm^{-1}):1620-1550, 1238 and 1020, and 755 example 11 piperidine, After using 15 ml of anhydrous

dichloromethane solutions of 3 g (it is the 3 time equivalent to [VIa]) of 3,4-methylenedioxyaniline and also reacting like Example 1, The insoluble matter was separated, dilute hydrochloric acid and water washed this, it recrystallized [chloroform], and 1.7 g of N-(3,4-methylenedioxyphenyl)-5,6-methylenedioxybenzo[b] franc 2-carboxamide of the fine yellow needle shape crystal was obtained (72% of yield).

[0085]melting point: -- 258-259 ** ultimate analysis: -- $C_{17}H_{11}NO_6$ theoretical-value (%):C and 62.77:H-3.41:N-4.31 actual-measurement (%):C -- a 62.59:H-3.41:N-4.35 ^{1}H-nuclear magnetic resonance spectrum. (Heavy DMSO) delta:10.28 (1H, s), 7.60 (1H, s), 7.43 (1H,d,J=2.0Hz), 7.25 (1H, s), 7.23 (1H, dd, J= 2.0, 8.4 Hz), 6.90 (1H,d,J=8.4Hz), 6.12 (2H, s, -OCH_2O-), 6.01 (2H, s, -OCH_2O-)

Instead of infrared-absorption-spectrum (KBr) nu (cm^{-1}):3410,1665,1580,1500, 1460,1318,1180,1035, and 940,925 example 122-(5,6-methylenedioxy) benzo[b] furancarboxylic acid [VIa], The output acquired by reacting like Example 1 is ******ed from ethyl acetate hexane using 2-(4,5-methylenedioxy) benzo[b] furancarboxylic acid [VIb]1.5g (7.3 millimol) obtained by the reference example 6, 1.35 g of the 1-[2-(4,5-methylenedioxy) benzo[b] franc carbonyl] piperidine of the colorless needle shape crystal was obtained (68% of yield).

[0086]melting point: -- 83-84 ** ultimate analysis: -- $C_{15}H_{15}NO_4$ theoretical-value (%):C and 65.92:H-5.53:N-5.13 actual-measurement (%):C -- a 66.10:H-5.47:N-5.21 ^{1}H-nuclear magnetic resonance spectrum. (Heavy chloroform) delta:7.15 (1H, s), 7.01 (1H,d,J=8.6Hz), 6.92 (1H,d,J=8.6Hz), 6.07 (2H, s, -OCH2 O-), 3.73 (4H, brs), 1.76 (6H, brs)

Instead of the infrared absorption spectrum (KBr) nu (cm^{-1}):2925,1620,1425,1260 and 1050,940 example 132-(5,6-methylenedioxy) benzo[b] furancarboxylic acid [VIa], The output acquired by reacting like Example 2 is ******ed from ethyl acetate hexane using 2-(4,5-methylenedioxy) benzo[b] furancarboxylic acid [VIb]2.0g (9.7 millimol) obtained by the reference example 6, 2.5 g of the 4-[2-(4,5-methylenedioxy) benzo[b] franc carbonyl] morpholine of the colorless needle shape crystal was obtained (93% of yield).

[0087]melting point: -- 127.4 -128.2 ** ultimate analysis: -- $C_{14}H_{13}NO_5$ theoretical-value (%):C and 61.09:H-4.76:N-5.09 actual-measurement (%):C -- a 61.07:H-4.65:N-5.11 ^{1}H-nuclear magnetic resonance spectrum. (Heavy chloroform) delta:7.27 (1H, s), 6.99 (1H,d,J=8.42Hz), 6.95 (1H,d,J=8.4Hz), 6.08 (2H, s, -OCH_2O-) and 3.85 (4H, brs), 3.80-3.75 (4H, m)

Instead of infrared-absorption-spectrum (KBr) nu (cm^{-1}):1630,1564,1425,1285, 1260,1190,1112,1052, and 990,795 example 142-(5,6-methylenedioxy) benzo[b] furancarboxylic acid [VIa], The output acquired by reacting like Example 3 is ******ed from ethyl acetate hexane using 2-(4,5-methylenedioxy) benzo[b] furancarboxylic acid [VIb]2.0g (9.7 millimol) obtained by the reference example 6, 2.4 g of the 4-[2-(4,5-methylenedioxy) benzo[b] franc carbonyl] thiomorpholine of the colorless needle shape crystal was obtained (85% of yield).

[0088]melting point: -- 125-126 ** ultimate analysis: -- $C_{14}H_{13}NO_4S$ theoretical-value (%):C and 57.72:H-4.50:N-4.81 actual-measurement (%):C -- a 57.73:H-4.46:N-4.85 ^{1}H-nuclear magnetic resonance spectrum. (Heavy chloroform) delta:7.23 (1H, s), 6.99 (1H,d,J=8.6Hz), 6.94 (1H,d,J=8.6Hz) and 6.08 (2H, s, -OCH_2O-), 4.08-4.03 (4H, m), 2.78-2.73 (4H, m)

Instead of the infrared absorption spectrum (KBr) nu (cm^{-1}):1625,1562,1430,1298 and 1265,1185,1050 example 152-(5,6-methylenedioxy) benzo[b] furancarboxylic acid [VIa], The output acquired by reacting like Example 4 is ******ed from ethyl acetate using 2-(4,5-methylenedioxy) benzo[b] furancarboxylic acid [VIb] 2.0g (9.7 millimol) obtained by the reference example 6, 1.5 g of N-methyl-(4,5-methylenedioxy) benzo[b] franc 2-carboxamide of the colorless needle shape crystal was obtained (69% of yield).
[0089]melting point: -- 183.0 -184.0 ** ultimate analysis: -- $C_{11}H_9NO_4$ theoretical-value (%):C and 60.28:H-4.14:N-6.39 actual-measurement (%):C -- a 60.11:H-4.21:N-6.41 ^{1}H-nuclear magnetic resonance spectrum. (Heavy chloroform) delta:7.40 (1H, s), 6.95 (2H, s), 6.62 (1H, brs, NH), 6.09 (2H, s, -OCH_2O-), 3.04 (3H,d,J=5.0Hz)

Instead of infrared-absorption-spectrum (KBr) nu (cm^{-1}):3280,1650,1590,1500, 1480,1288,1190,1060, and 920 example 162-(5,6-methylenedioxy) benzo[b] furancarboxylic acid [VIa], The output acquired by reacting like Example 5 is ******ed from ethyl acetate hexane using 2-(4,5-methylenedioxy) benzo[b] furancarboxylic acid [VIb]2.0g (9.7 millimol) obtained by the reference example 6, 2.2 g of N-isobutyl-(4,5-methylenedioxy) benzo[b] franc 2-carboxamide of the colorless needle shape crystal was obtained (87% of yield).
[0090]melting point: -- 112-113 ** ultimate analysis: -- $C_{14}H_{15}NO_4$ theoretical-value (%):C and 64.36:H-5.79:N-5.36 actual-measurement (%):C -- a 64.31:H-5.90:N-5.36 ^{1}H-nuclear magnetic resonance spectrum. (Heavy chloroform) delta:7.40 (1H, s), 6.96 (1H, d, J= 9.6 Hz), 6.95 (1H,d,J=9.6Hz), 6.65 (1H, brs), 6.09 (2H, s, -OCH_2O-), 3.31 (2H,t,J=6.2Hz), 1.93 (1H, sep, J= 6.8 Hz), 1.01 (6H,d,J=6.8Hz)

Instead of infrared-absorption-spectrum (KBr) nu (cm^{-1}):3340,2960,1650,1598, 1480,1290,1190,1050, and 915 example 172-(5,6-methylenedioxy) benzo[b] furancarboxylic acid [VIa], The output acquired by reacting like Example 8 is ******ed from ethyl acetate hexane using 2-(4,5-methylenedioxy) benzo[b] furancarboxylic acid [VIb]2.0g (9.7 millimol) obtained by the reference example 6, N of colorless prism ** -(3-methoxy propyl)- (4,5-methylenedioxy) 2.1 g of benzo[b] franc 2-carboxamide was obtained (78% of yield).
[0091]melting point: -- 92.7 -93.4 ** ultimate analysis: -- $C_{14}H_{15}NO_5$ theoretical-value (%):C and 60.64:H-5.45:N-5.05 actual-measurement (%):C -- a 60.60:H-5.37:N-5.09 ^{1}H-nuclear magnetic resonance spectrum. (Heavy chloroform) delta:7.30 (1H, s), 7.16 (1H, brs, NH), 6.96 (1H, d, J= 9.0 Hz), 6.94 (1H, d, J= 9.0 Hz), 6.08 (2H, s, -OCH_2O-), 3.59 (2H,q,J=6.1Hz), 3.56 (2H,t,J=5.7Hz), 3.41 (3H, s), 1.91 (2H, quint, J= 6.1 Hz)

Instead of infrared-absorption-spectrum (KBr) nu (cm^{-1}):3130,1665,1595,1479, 1280,1185,1100,1045, and 908 example 182-(5,6-methylenedioxy) benzo[b] furancarboxylic acid [VIa], The output acquired by reacting like Example 9 is ******ed from ethyl acetate hexane using 2-(4,5-methylenedioxy) benzo[b] furancarboxylic acid [VIb]2.0g (9.7 millimol) obtained by the reference example 6, N of a colorless needle shape crystal -(3-isopropoxy propyl)- (4,5-methylenedioxy) 2.5 g of benzo[b] franc 2-carboxamide was obtained (84% of yield).
[0092]melting point: -- 96.3 -97.0 ** ultimate analysis: -- $C_{16}H_{19}NO_5$ theoretical-value (%):C and 62.94:H-6.27:N-4.59 actual-measurement (%):C -- a 62.94:H-6.13:N-4.63 ^{1}H-nuclear magnetic resonance spectrum. (Heavy chloroform) delta:7.67 (1H, brs, NH), 7.36 (1H, s), 6.93 (1H,d,J=8.9Hz), 6.91 (1H,d,J=8.9Hz), 6.07 (2H, s, -OCH_2O-), 3.70-3.56 (5H, m), 1.89 (2H, quint, J= 5.75 Hz), 1.26 (6H,d,J=6.0Hz)

Instead of infrared-absorption-spectrum (KBr) nu (cm^{-1}):3380,2980,1670,1600, 1522,1500,1478,1285, and 1050,778 example 192-(5,6-methylenedioxy) benzo[b] furancarboxylic acid [VIa], The output acquired by reacting like Example 10 is ******ed from ether using 2-(4,5-methylenedioxy) benzo[b] furancarboxylic acid [VIb]2.0g (9.7 millimol) obtained by the reference example 6, 2.6 g of the 1-(2-methoxypheny)-4-[2-(4,5-methylenedioxy) benzo[b] franc carbonyl] piperazines of the colorless needle shape crystal were obtained (94% of yield).

[0093]melting point: -- 151-152 ** ultimate analysis: -- $C_{21}H_{20}N_2O_5$ theoretical-value (%):C and 66.31:H-5.30:N-7.36 actual-measurement (%):C -- a 66.11:H-5.23:N-7.32 ^{1}H-nuclear magnetic resonance spectrum. (Heavy chloroform) delta:7.25 (1H, s), 7.10-6.88 (6H, m), 6.09 (2H, s, -OCH_2O-), 4.03 (4H, brs), 3.90 (3H, s, OCH3), 3.15 (4H,t,J=5.2Hz)

Instead of the infrared absorption spectrum (KBr) nu (cm^{-1}):1615,1498,1422,1273 and 1255,1235,1015,738 example 202-(5,6-methylenedioxy) benzo[b] furancarboxylic acid [VIa], The output acquired by reacting like Example 2 is ******ed from ether hexane using 2-(6,7-methylenedioxy) benzo[b] furancarboxylic acid [VIc] 2.0g (9.7 millimol) obtained by the reference example 7, 2.4 g of the 4-[2-(6,7-methylenedioxy) benzo[b] franc carbonyl] morpholine of the colorless needle shape crystal was obtained (90% of yield).

[0094]melting point: -- 119.7 -120.3 ** ultimate analysis: -- $C_{14}H_{13}NO_5$ theoretical-value (%):C and 61.09:H-4.76:N-5.09 actual-measurement (%):C -- a 60.99:H-4.85:N-5.09 ^{1}H-nuclear magnetic resonance spectrum. (Heavy chloroform) delta:7.35 (1H, s), 7.14 (1H,d,J=8.4Hz), 6.91 (1H,d,J=8.4Hz) and 6.10 (2H, s, -OCH_2O-), and 3.91-3.75 (8H, m)

Instead of the infrared absorption spectrum (KBr) nu (cm^{-1}):1658,1625,1475,1260 and 1115,1060,1040,918 example 212-(5,6-methylenedioxy) benzo[b] furancarboxylic acid [VIa], The output acquired by reacting like Example 4 is ******ed from ethyl acetate using 2-(6,7-methylenedioxy) benzo[b] furancarboxylic acid [VIc] 2.0g (9.7 millimol) obtained by the reference example 7, 1.7 g of N-methyl-(6,7-methylenedioxy) benzo[b] franc 2-carboxamide of colorless prism ** was obtained (80% of yield).

[0095]melting point: -- 169.0 -170.0 ** ultimate analysis: -- $C_{11}H_9NO_4$ theoretical-value (%):C and 60.28:H-4.14:N-6.39 actual-measurement (%):C -- a 60.19:H-4.20:N-6.43 ^{1}H-nuclear magnetic resonance spectrum. (Heavy chloroform) delta:7.42 (1H, s), 7.15 (1H,d,J=8.2Hz), 6.91 (1H,d,J=8.2Hz), 6.64 (1H, brs, NH), 6.10 (2H, s, -OCH_2O-), 3.03 (3H,d,J=5.0Hz)

Instead of the infrared absorption spectrum (KBr) nu (cm^{-1}):3400,1645,1490,1475 and 1260,1185,1038,918 example 222-(5,6-methylenedioxy) benzo[b] furancarboxylic acid [VIa], 2-(6,7-methylenedioxy) benzo[b] furancarboxylic acid [VIc]2.0g (9.7 millimol) obtained by the reference example 7 is used, The output acquired by reacting like Example 5 was given to the silica gel column, it was eluted by ethyl acetate hexane (1:3), and 2.5 g of N-isobutyl-(6,7-methylenedioxy) benzo[b] franc 2-carboxamide of the colorless oily matter was obtained (98% of yield).

[0096]Ultimate analysis : The $C_{14}H_{15}NO_4$ theoretical-value (%):C,64.36:H,5.79:N,5.36 actual-measurement (%):C,64.23:H,5.77:N,5.32 ^{1}H-nuclear magnetic resonance spectrum (heavy chloroform) delta:7.43 (1H, s), 7.16 (1H, d, J= 8.4 Hz), 6.91 (1H, d, J= 8.4 Hz), 6.66 (1H, brs, NH), 6.11 (2H, s, -OCH_2O-), 3.30

(2H,t,J=6.5Hz), 1.92 (1H, sep, J= 6.7 Hz), 1.00 (6H,d,J=6.8Hz)

Instead of the infrared absorption spectrum (chloroform) nu (cm^{-1}):3450,2975,1670,1605 and 1525,1486,1270,1072 example 232-(5,6-methylenedioxy) benzo[b] furancarboxylic acid [VIa], The output acquired by reacting like Example 1 is ******ed from ethyl acetate using 3-[2-(5,6-methylenedioxy) benzo[b] franc] propenoic acid [VId]1.5g obtained by the reference example 11, 1.04 g of 1-[3-(5,6-methylenedioxybenzo[b] franc 2-yl)-1-oxo 2-propenyl] piperidine of the yellow needle shape crystal was obtained (54% of yield).

[0097]Melting point : The 151.6 -152.6 ** ^{1}H-nuclear magnetic resonance spectrum (heavy chloroform) delta:7.49 (1H, d, J= 15.2 Hz), 6.95 (1H,d,J=15.2Hz), 6.95 (1H, s), 6.91 (1H, s), 6.74 (1H, s), 6.00 (2H, s, -OCH_2O-), 3.64 (4H, brs), 1.66 (4H, brs), 1.61 (2H, s)

Instead of the infrared absorption spectrum (KBr) nu (cm^{-1}):2940,1640,1590,1460 and 1315,1210,940,840 example 242-(5,6-methylenedioxy) benzo[b] furancarboxylic acid [VIa], The output acquired by reacting like Example 2 is ******ed from ethyl acetate hexane using 3-[2-(5,6-methylenedioxy) benzo[b] franc] propenoic acid [VId]2.0g obtained by the reference example 11, 1.7 g of 4-[3-(5,6-methylenedioxybenzo[b] franc 2-yl)-1-oxo 2-propenyl] morpholine of yellow prism ** was obtained (64% of yield).
[0098]melting point: -- 196.2 -197.5 ** ultimate analysis: -- $C_{16}H_{15}NO_5$ theoretical-value (%):C and 63.78:H-5.02:N-4.65 actual-measurement (%):C -- a 63.54:H-5.00:N-4.48 ^{1}H-nuclear magnetic resonance spectrum. (Heavy chloroform) delta:7.54 (1H,d,J=15Hz), 6.95 (1H, s), 6.92 (1H, s), 6.89 (1H,d,J=15Hz), 6.79 (1H, s), 6.01 (2H, s, -OCH_2O-), 3.74 (8H, brs)

Instead of the infrared absorption spectrum (KBr) nu (cm^{-1}):1645,1405,1464,1318 and 1170,1038 example 252-(5,6-methylenedioxy) benzo[b] furancarboxylic acid [VIa], The output acquired by reacting like Example 3 is ******ed from ethyl acetate hexane using 3-[2-(5,6-methylenedioxy) benzo[b] franc] propenoic acid [VId] 2.0g obtained by the reference example 11, 1.0 g of 4-[3-(5,6-methylenedioxybenzo[b] franc 2-yl)-1-oxo 2-propenyl] thiomorpholine of yellow prism ** was obtained (38% of yield).
[0099]melting point: -- 177.3 -178.5 ** ultimate analysis: -- $C_{16}H_{15}NO_4S$ theoretical-value (%):C and 60.55:H-4.76:N-4.41 actual-measurement (%):C -- a 60.36:H-4.79:N-4.37 ^{1}H-nuclear magnetic resonance spectrum. (Heavy chloroform) delta:7.52 (1H, d, J= 15 Hz), 6.95 (1H, s), 6.92 (1H, s), 6.89 (1H,d,J=15Hz), 6.78 (1H, s), 6.01 (2H, s, -OCH_2O-), 3.99 (4H, brs), 2.72-2.67 (4H, m)

Instead of the infrared absorption spectrum (KBr) nu (cm^{-1}):1648,1600,1465,1422 and 1320,1170,1035 example 262-(5,6-methylenedioxy) benzo[b] furancarboxylic acid [VIa], The output acquired by reacting like Example 5 is ******ed from ether using 3-[2-(5,6-methylenedioxy) benzo[b] franc] propenoic acid [VId]2.0g obtained by the reference example 11, 1.48 g of N-isobutyl-3-[2-(5,6-methylenedioxy) benzo[b] franc]-2-propene amide of fine xanthelasma-like ** was obtained (60% of yield).

[0100]Melting point : The 176.5 -177.5 ** ^{1}H-nuclear magnetic resonance spectrum (heavy chloroform) delta:7.46 (1H, d, J= 15.2 Hz), 6.93 (1H, s), 6.91 (1H, s), 6.76 (1H, s), 6.44 (1H,d,J=15.2Hz), 6.00 (2H, s, -OCH_2O-), 5.67 (1H, brs, NH), 3.23 (2H,t,J=6.4Hz), 1.85 (1H, sep, J= 6.7 Hz), 0.96 (6H,d,J=6.8Hz)

Instead of infrared-absorption-spectrum (KBr) nu (cm^{-1}):3350,2950,1660,1620, 1460,1320,1165,940, and

842 example 272-(5,6-methylenedioxy) benzo[b] furancarboxylic acid [VIa], The output acquired by reacting like Example 9 is ******ed from ethyl acetate hexane using 3-[2-(5,6-methylenedioxy) benzo[b] franc] propenoic acid [VId]2.0g obtained by the reference example 11, 1.6 g of N-isopropoxy propyl-3-[2-(5,6-methylenedioxy) benzo[b] franc]-2-propene amide of the yellow needle shape crystal was obtained (56% of yield).

[0101]melting point: -- 123.6 -124.6 ** ultimate analysis: -- $C_{18}H_{21}NO_5$ theoretical-value (%):C and 65.24:H-6.39:N-4.23 actual-measurement (%):C -- a 65.14:H-6.37:N-4.24 ^{1}H-nuclear magnetic resonance spectrum. (Heavy chloroform) delta:7.45 (1H, d, J= 15 Hz), 6.94 (1H, s), 6.91 (1H, s), 6.75 (1H, s), 6.41 (1H, brs, NH), 6.37 (1H,d,J=15Hz), 6.00 (2H, s, -OCH_2O-), 3.66-3.47 (5H, m), and 1.82 (2H, quint, J= 6.0 Hz) and 1.20 (6H,d,J=6.0Hz)

The experiment was presented after making infrared-absorption-spectrum (KBr) nu (cm^{-1}):3252-1668, 1612, 1562, 1462, 1322 and 1168, and an example of 942 experiments male ICR system mouse (six weeks old) abstain from food for 24 hours. It was suspended in gum arabic liquid 5%, and medicated intraperitoneal with acetaminophen at a rate of 0.4 g/kg. The sample compound shown in a table was suspended in gum arabic liquid 5%, and was administered orally to 30 quotas which prescribe acetaminophen for the patient at a rate of 30 mg/kg (compound of Example 21), or 100 mg/kg (compounds other than example 21).

[0102]It collected blood, 24 hours after prescribing acetaminophen for the patient, and the inhibiting activities of ALT in plasma were measured with enzymatic process. A result is shown in a table. The result in the example of an experiment was all significant at the test of significance $p< 0.1$ (compound of Example 19), or $p< 0.01$ (compounds other than example 19) (Dunnett).

[0103]

[Table 1]

表１

化　合　物	ＡＬＴ抑制率（％）
実施例 4	９９
実施例 5	９９
実施例 6	９９
実施例 7	９５
実施例１０	９４
実施例１５	９９
実施例１６	９９
実施例１８	９７
実施例１９	８３
実施例２１	１００
実施例２２	９２

The compound of an example controls the rise of the ALT value in plasma notably by internal use so that clearly from the result shown in a table.

[0104]After mixing uniformly example milk sugar of pharmaceutical preparation 77 weight section, hydroxypropylcellulose 10 weight section, light-anhydrous-silicic-acid 1 weight section, the amount part of magnesium stearate duplexs, and compound 10 weight section of Example 21, compression molding is carried out and a tablet is obtained.

[Translation done.]